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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
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DATE: June 27, 1978

SUBJECT: N-nitrosoglyphosate. Toxicology Studies, Accession No. 229785, submitted by Monsnto, 5/6/77 (RD 131, Special Report 478, L. H. Hannah, et al). Toxicology Branch evaluation of Petitioner's (3/20 & 5/24/78) comme ts on EPA (2/13 & 4/20/78) letters concerning them; glyphosate PP 5F1560 (& other blyphosate PP's)

FROM: Toxicology Branch, Roland A. Gessert, D.V.M.

TO: Mr. Robert Taylor, Product Manager # 25

PP No. 5F1560
(Reg. No. 524-308)

Monsanto Agricultural Prods.
St. Louis, Missouri

In the absence of Dr. Mary L. Quaife who has conducted most of the data reviews on glyphosate and its impurity, N-nitrosoglyphosate (NNG), I have been requested to assess Dr. Quaife's review dated June 14, 1978 in light of Chemistry Branch's (Dr. M. Nelson) review of the latest data reviewed by Dr. Quaife.

Dr. Quaife judged the Ames type in vitro test to be CORE-minimum, while criticizing the 100 ug level of NNG used in the upper level as being less than the 500 ug level recommended by Ames for a weak mutagen.

Dr. Quaife, likewise judged the mouse dominant lethal mutagenicity test to be CORE-minimum and acceptable, while criticizing the 5 and 10 mg/kg IP dose as low compared to the high oral LD_{50} (5000 to 7000 mg/kg) in the rat.

Regarding the rabbit teratology test, Dr. Quaife judged the study to be CORE supplementary, in that the test doses used were low compared with the rat acute oral toxicity, only two dose levels were used, doses were low relative to the rat oral LD_{50}, and no positive control was used. Also, Dr. Quaife prefers the Mann-Whitney method of statistical analysis recommended by her reference, while the applicant used the "one-tail Fisher's exact test."

It previously has been recognized that no residues of NNG will appear in raw agricultural commodities treated with technical glyphosate. The issue, therefore, has been whether the low levels of NNG appearing as an impurity in technical glyphosate will be harmful to workers applying the pesticide.

The results of an application study previously submitted by Monsanto measured actual amounts of glyphosate and NNG to which an applicator may be exposed when loading and applying the pesticide by various means. These results demonstrated exposure to glyphosate to be essentially nil, and to NNG to be non-existant. (Review attached.)

At present EPA have no specific official guidelines for toxicity testing. It is expected that guidelines will be published for comment soon. And when they are published, they will be just as the title indicates: Guidelines.And all studies need not be performed in an identical manner. Dr. Quaife prefers teratology studies be conducted as outlined by Collins in "New Concepts in Safety Evaluation," edited by M. Mehlman, et al; John Wiley & Sons, N.Y., Chapt. 6, pp 155-175. Others in EPA prefer ENVIRONMENT & BIRTH DEFECTS, by

James E. Wilson, Academic Press, N.Y., 1973. The important thing is that the studies demonstrate what they are designed to demonstrate: whether the product is safe, or unsafe.

Dr. M. Nelson, Chemistry Branch, has reviewed glyphosate (ROUNDUP) and NNG (summary attached), and again defers to Toxicology Branch the question of safety. She states the maximum calculated residues of NNG on raw agricultural commodities, assuming that all of the NNG present in the applied formulation is found on the harvested commodity, is in the 10-20 ppb range. Due to the photosensitivity of NNG to ultra violet light, actual residues in food items would be expected to be appreciably less than these amounts.

Data based on activity measurements from tracer studies with ^{14}C-glyphosate indicate maximum hypothetical residues of 0.001 - 0.007 ppm (less than 1 to 7 ppb). And in our concern with safety to the applicator, the essentially nil exposure would result in zero exposure to NNG.

In consideration of these factors, I would consider the mutagenicity and teratology studies reviewed by Dr. Quaife to be adequate to demonstrate safety of technical glyphosate (and any NNG present, if any) to the applicator, and for any raw agricultural commodity treated with technical glyphosate.

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